REMARKS

Prior to entry of the foregoing amendments, claims 17 to 23 were pending. Claims 17 to 23 have been cancelled without prejudice or disclaimer, and claims 32 to 67 have been added. Accordingly, claims 32 to 67 will be pending for examination on the merits.

Objections to the specification

The Examiner refers to 37 CFR §§ 1.58(a) and 1.83(a) in support of a requirement to delete sequence data from the specification. These sections were amended in 2004, long after the instant application was filed. The instant application was fully in compliance with the requirements of 37 CFR §§ 1.58(a) and 1.83(a) in force at the time of filing of the application.

Restriction requirement

With regard to the restriction requirement previously imposed, the Examiner has rejoined Groups II and III with Group I. Applicant submits that each of the present claims falls within Groups I, II and/or III. With respect to the election of species requirement, applicant reiterates below the prior election and set forth those claims which read on the elected species:

i. the gene III protein with an additional methionine residue at the N-terminus as the modified variant of a wild type protein. All claims read on this species.

ii. 5 histidines and 1 cysteine as the one to six additional amino acid residues. All claims read on this species.

iii. a vector for expression of Fab antibody fragments, comprising two nucleic acid sequences encoding the VH-CH and the VL-CL chains as the vector. All claims read on this species.

iv. *E. coli* as the host cell. Claims 32 to 41 and 49 to 63 read on this host cell.

Support for new claims

The new claims are supported by the specification as originally filed. Claim 32 is supported in the specification as filed, *inter alia*, on page 12, lines 7 to 8; on page 10, lines 9 to 17 and on page 26, lines 25 to page 27, line 2. The term "modified" has been deleted from the term "modified variant." Furthermore, the term "second" in the term "second cysteine residue" has also been deleted. Claim 33 is supported in the specification as filed, *inter alia*, on page 4, lines 6 to 12 and on page 8, last paragraph. Claim 34 is supported, e.g., as shown for claim 32 and on page 6, penultimate and last paragraphs and by Example 1. The term "truncated variant" has been amended to read

"truncated portion". Claim 35 is supported, *inter alia*, as shown above for claim 33. Support for claims 36 and 37 can be found in the specification as filed, e.g., on page 10, last paragraph to page 11, first paragraph. Claims 38 and 39 find support, e.g., on page 12, third paragraph and claims 40 and 41 are, *inter alia*, supported by the subject matter disclosed on page 12, first paragraph. Support for claim 42 can be found, in addition to the support already cited for claim 32 above, for example on page 11, last paragraph. Claim 43 is supported, e.g., as shown for claim 33, above. For claim 44 and 45, support can be found for example on page 5, lines 13 to 24. Support for claims 46 to 48 is, *inter alia*, as shown for claim 40. Support for any one of claims 49 to 56 is as shown, *inter alia*, for claim 32 above, and for claims 56 through 62 as shown above, e.g., for claim 38. Claim 63 is supported as shown above for claim 33. Claim 64 is supported in the specification as filed, *inter alia* and implicitly, on page 11, last paragraph in combination with the disclosure content of page 10, last paragraph to page 11, first paragraph. Support for claim 63 can be found, e.g., on page 10, first paragraph and page 12, first paragraph. Finally, support for claims 66 and 67 can be found, *inter alia*, as already shown above for claim 40

Information Disclosure Statement:

Based on the Examiner's statements that WO 94/00588 and WO 97/40141 could not be found in the parent application, applicant will submit hard copies of these publications under separate cover. Consideration of these publications is respectfully requested.

Rejections under 35 U.S.C. § 102(b):

Claims 17-20 and 22 are rejected as anticipated by Kay et al. U.S. Patent 5,747,334 ("Kay"). Claims 17 to 22 are rejected as anticipated by Deem et al. U.S. Patent 6,341,256 B1 ("Deem"), and claims 17 to 22 are rejected as anticipated by U.S. Patent No. 6,309,642 issued to Cutler et al. ("Cutler"). These rejections are moot in light of the cancellation of the relevant claims, however, the analysis below sets forth why added claims 32 to 67 are free of the cited art.

Kay does not anticipate the claimed invention as recited in new claims 32 to 67.

Kay purports to teach a method for producing novel and/or improved heterofunctional binding fusion proteins termed Totally Synthetic Affinity reagents (TSARs). See Abstract. Kay furthermore discloses a library of recombinant vectors in which each vector encodes a plurality of heterofunctional fusion proteins where the

library may be screened to identify a heterofunctional fusion protein having specificity for a ligand of choice. See claim 1, column 171.

In particular, Kay states that each heterofunctional fusion protein of the library might comprise at least one disulfide bond forming at least one cystine thereby allowing for the formation of at least one loop conformation in each expressed heterofunctional fusion protein eventually resulting in a semirigid conformation in the expressed peptide. See claim 8, column 19, lines 14 to 29 and column 16, lines 1 to 4. The heterofunctional fusion proteins might be attached to the pIII protein of the phage M13 as might be derived from Figures 1 D and 1 E.

However, Kay fails to teach each and every element of the invention set forth in new claims 32 to 67. Kay does not teach a bacterial host cell that comprises a combination of two different vectors as recited in new claim 32, where a first vector comprises a nucleic acid sequence encoding a variant of a wild type phage coat with an additional cysteine residue and a second vector comprises one or more nucleic acid sequences encoding a (poly)peptide/protein comprising a second cysteine residue.

The same reasoning applies, *mutatis mutandis*, to the host cell as disclosed in new claims 34 to 41, 49 to 63, 66 and 67 and also to the vector recited in new claims 42 to 48 and the nucleic acid sequence of new claim 64 and 65. The vector comprises a nucleic acid sequence encoding a variant of a wild type phage coat with an additional cysteine residue and one or more nucleic acid sequences encoding a (poly)peptide/protein comprising a second cysteine residue. The nucleic acid sequence codes for a phage coat protein and for a (poly)peptide/protein each comprising a cysteine. For at least these reasons, claims 34, 42, 49, 64, 66 and 67 are novel over Kay and, accordingly, the claims that depend from these claims also are novel over Kay.

Deem does not anticipate the claimed invention as recited in new claims 32 to 67.

Deem teaches a method of determining a consensus pharmacophore for binding to a target molecule at a temperature of interest. The method comprises determining a consensus structure for the potential pharmacophores. For this purpose, Deem provides a computer implemented modelling and simulation method to determine a highly accurate consensus structure. See columns 5 and 6 of Deem.

In particular, Deem discloses the screening of a diversity library to select binders which specifically bind to a target of interest. The library members should all have constrained structures and bind to the target molecule in a specific manner. The constrained structures are achieved by e.g. internal linkers, such as disulfide bonds. See columns 5 and 6 of Deem.

Deem, however, also differs from the claimed invention as recited in new claims 32 to 67 for the reasons set forth above for Kay. Accordingly, Deem does not disclose a host bacterial cell, a vector or a nucleic acid as recited in new claims 26, 34, 41, 56, 58 and 59, and therefore the new claims also are novel with respect to Deem.

Cutler does not anticipate the claimed invention as recited in new claims 32 to 67.

Cutler teaches a composition, pharmaceutical composition, vaccine and method for the treatment of candidiasis (an infection caused by the fungus *Candida*). The composition includes phosphomannan of *C. albicans*, peptide mimotopes of phosphomannan epitopes, or polynucleotides encoding the peptide mimotopes. Monoclonal antibodies for use in immunization are also provides. See Abstract.

Cutler provides a vaccine for treatment of candidiasis comprising a pharmaceutically effective amount of peptides that are specific structural mimics (mimotopes) or epitopes specific to the mannan portion of the phosphomannan complex of *Candida*. See column 4, lines 13 to 18. More specifically, nonapeptides (equalling the mimotopes mentioned above) having specificity against the monoclonal antibody MAb B6.1 are disclosed together with DNA constructs encoding the nonapeptides. See column 4, lines 19 to 47.

Experimentally, the nonapeptides were retrieved and discovered from a "phage display peptide library" ("PDPL") by displaying the library against the above mentioned monoclonal antibody Mab B6.1. See column 8, lines 45 to 48. The 27-mer oligonucleotides encoding the retrieved nonapeptides were then primed to the end of the pIII protein and used for further analysis, such as for further phage display against the MAb B6.1, dot blot analyses etc. See column 10, lines 20 to 32. Then, a specific nonapeptide displayed by a specific phage clone was chosen for synthesis and used in inhibition studies. To this specific nonapeptide, subsequently, a GPP tether derived from the pIII protein and one additional cysteine residue was added – resulting in an 13-mer peptide – to facilitate the coupling of the 13-mer peptide to a carrier protein, such as KLH. See column 13, lines 35 to 45.

However, by this stage in the method, the pIII protein was no longer attached to the 13-mer construct. See Examples 1 and 2 of the specification and, in particular, Example 4, column 13, lines 35 to 45. Hence, the 13-mer construct containing the Cys at the end is NOT coupled to the phage pIII protein. By contrast, the instant claims require that a Cysteine be present in a variant of a wild type coat protein of a bacteriophage or in a wild type coat protein or truncated variant thereof. Accordingly, Cutler does not teach each and every element of the claimed invention and does not anticipate the instant claims. Moreover, Cutler does not disclose a host bacterial cell

comprising two vectors as recited in the new claims, nor does Cutler disclose any of the subject-matter recited in those claims.

35 U.S.C. § 103(a):

Claims 17-22 are rejected as obvious over Kay in light of Kipriyanov, and also are rejected as obvious over Cutler in view of Jespers. These rejections are moot in light of the cancellation of claims 17-22 but, to the extent that the Examiner would seek to apply the rejections to the added claims, applicant respectfully traverses.

When combining references to make out a *prima facie* case of obviousness, the examiner is obliged to show by citation to specific evidence in the cited references that (i) the combination of references discloses all of the claim elements recited in the claims at issue, (ii) there was a suggestion/motivation to make the combination and (iii) there was a reasonable expectation that the combination would succeed. Both the suggestion/motivation and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *see also* MPEP §§ 2142-43 (August 2001). Thus, the examiner must provide evidentiary support based upon the contents of the prior art to support all facets of the rejection, rather than just setting forth conclusory statements, subjective beliefs or unknown authority. *See In re Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002). In the instant case, the Examiner has failed to show that the cited references describe all of the elements recited in the instant claims, has failed to describe why one of ordinary skill in the art would have been motivated to combine the cited references, and has failed to provide appropriate evidence that there was a reasonable expectation of success in making the combination. Accordingly, no *prima facie* case of obviousness exists and the the rejection should be withdrawn.

With respect to the rejection over Kay in view Kipriyanov, the basis of the rejection appears to be that one of ordinary skill in the art would have been motivated to modify the teachings of Kay by modifying the phage-display vectors of Kay containing one or more cysteine residues with the immunoglobulin fragments taught by Kipriyanov (see pages 15 thorough 17 of the Office Communication).

A skilled worker, upon reading Kay, would immediately appreciate that Kay incorporated the additional cysteine residues into the TSARs (heterofunctional fusion proteins) solely to create a library of polypeptides where the polypeptides have some degree of conformational rigidity in their structure. Simply put, the use of a cysteine for the purpose of structure stability does not suggest a host cell comprising the features

according to any one of claims 26 to 33, 41 to 55, 58 and 59, or a vector according to claim claims 34 to 40 or a nucleic acid sequence according to claims 56 and 57.

Kiprianov fails to remedy these deficiencies. Morevoer, there would not have been any motivation to combine Kay with Kipriyanov, nor would there have been a reasonable expectation of success in the combination. Whereas Kay describes a library which expresses proteins rendered semi-rigid via Cysteine disulfide bonds, Kipriyanov discloses recombinant scFvs fragments carrying C-terminal Cysteine residues which can be used for the production of bivalent and biotinylated miniantibodies. Thus, the rationale for employing a cysteine residue in Kay ("semi-rigidity") is different than the rationale that Kipriyanov employs ("production of bivalent and biotinylated miniantibodies"). These distinct rationales would not only not motivate a skilled artisan to combine the two documents but would also not provide any reasonable expectation of success in the combination. Accordingly, applicant respectfully urges that no prima facie obviousness case exists.

With respect to the rejection over Cutler in view of Jespers, the basis of the rejection appears to be that one of ordinary skill in the art would have been motivated to modify the teachings of Cutler by modifying the alleged gene III-cysteine phage display vector with the cysteine-antibody fragment construct taught by Jespers (see pages 17 through 19 of the Office Communication).

As set forth above, Cutler does not teach every element of the new claims. Nor does Cutler teach or suggest the instantly claimed invention. In particular, as noted above, in Cutler the cysteine residue is coupled to selected nonapeptides after the nonapaptides are displayed in a phage library. In contrast, the presently claimed invention teaches that a cysteine residue is part of the phage coat protein; another cysteine is comprised in the (poly)peptide to be displayed or is expressed at the time of phage coat protein expression. Cutler discloses a phage display system which is, functionally speaking, entirely independent of any cysteine residue whatsoever. Jespers can do nothing to remedy this fatal deficiency. Accordingly, neither of the cited references, alone or in combination, teaches or suggests the instantly claimed invention. Accordingly, applicant respectfully urges that no prima facie obviousness case exists with respect to Cutler in combination with Jespers.

35 U.S.C. § 112, first paragraph (written description):

Previous claims 17 to 22 are rejected under 35 U.S.C 112, first paragraph, for lack of written description. This rejection is moot in light of the cancellation of claims 17-22. However, to the extent that the Examiner might seek to apply these grounds of

rejection to the new claims, the analysis below sets forth why the new claims fully comply with § 112, first paragraph.

As applicant understands the rejection, the Examiner asserts that applicant was not in possession of the entire scope of the claimed invention. In particular, the terms "modified variant of a wild type coat protein of a bacteriophage" and "one or more peptides" are rejected as not being sufficiently described. The rejection is based, *inter alia*, on the assumption that the claims recite functional language (i.e. the terms "causes or allows the incorporation of phage coat protein into the phage coat" - with special focus on the term "causes or allows" - and "one or more parts of said wild type coat protein" with respect to the definition of the term "modified variant of a wild type coat protein..."; and "for purification and/or detection purposes" with respect to the term "one or more peptides"). In addition, the Examiner states that the term "fragments" is too broad and, in particular, the term "functional fragment" is rejected on the grounds that the application allegedly does not show, for example, when an immunoglobulin is functional.

Additionally, the Examiner states that the specification provides only limited examples ("specification only provides wild type coat proteins of filamentous phage including pIII, pVI, pVII, pVIII, pIX") and cites the experiments as exemplified in the Examples 1 and 2 (see Office Action page 11, last paragraph to page 12, first paragraph). These examples, according to the Examiner, allegedly would not put the applicant into a position for claiming generic disclosures.

Finally, the Examiner states that no common structural attributes are disclosed that link together the claimed nucleic acid sequences or no common attributes or characteristics are disclosed that identify all members of the genus.

The Examiner relies on *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997), see Office Action page 5, last paragraph, which held that an invention requires a precise definition, such as by structure, formula [or] chemical name. The Examiner states that the Lilly holding, although directed to DNA compounds, might be transferred to any compound or genus of compounds, which requires a representative sample of compounds or a showing of sufficient identifying characteristics, to demonstrate possession of the genus. Practically speaking, a genus of cDNAs might be achieved by means of a recitation of a representative number of cDNAs or a recitation of structural features common to members of the genus.

Without acquiescing in the Examiner's conclusion based on the 'Lilly' case, applicant kindly directs the Examiner's attention to the recently published decision of the United States Court of Appeal for the Federal Circuit, *Falkner v. Inglis*, 05-1324, ** F.3d *** (Fed. Cir. May 26, 2006). In particular, reference is made to section C of said

decision dealing with the Written Description requirement. The Court's conclusions with respect to the adequacy of the written description requirement can be summarized as follows:

1.) Examples are not required
2.) Actual reduction to practice is not required
3.) Recitation of known structure is not required.

In Falkner, the claims at issue were directed to vaccines derived from a poxvirus in which an "essential region" of the virus was deleted. However, Inglis neither reduced the claimed invention to practice nor incorporated by reference any literature that described the DNA sequence of the poxvirus genome or the locations of the "essential regions." Rather, Inglis as serted that prior art describing essential regions of the poxvirus was well known in the art. The court declared that the patent claims satisfied the written description requirement:

> A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation.

The court went on to hold that:

> an actual reduction to practice is not required for written description. See Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 926 (Fed. Cir. 2004) ("We of course do not mean to suggest that the written description requirement can be satisfied only by providing a description of an actual reduction to practice. Constructive reduction to practice is an established method of disclosure . . . ."). Rochester, moreover, is consistent with Supreme Court precedent. In the context of interpreting 35 U.S.C. § 102(b), the Court held that "[t]he word 'invention' must refer to a concept that is complete, rather than merely one that is 'substantially complete.'" Pfaff v. Wells Elecs., 525 U.S. 55, 66 (1998). It then proceeded to make clear that although "reduction to practice ordinarily provides the best evidence that an invention is complete. . . . it does not follow that proof of reduction to practice is necessary in every case." Id. (emphasis added). Thus, to the extent that written description requires a showing of "possession of the invention," Capon, 418 F.3d at 1357 (emphasis added), Pfaff makes clear that an invention can be "complete" even where an actual reduction to practice is absent. The logical predicate of "possession" is, of course, "completeness."

(Emphasis added) Pertinent to the written description rejection in the present case is the court's rationale behind its holding that a recitation of known structure is not required with respect to inventions involving DNA:

> Falkner argues, *inter alia*, that the Inglis specifications do not adequately describe the poxvirus invention, in light of Eli Lilly, because they do not describe the "essential regions" of any poxvirus. 119 F.3d 1559. We note, in addition, that Inglis did not attempt to incorporate by reference any literature that described the DNA sequence of the poxvirus genome and the locations of the "essential regions." However, it is the binding precedent of this court that Eli Lilly does not set forth a per se rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art. See Capon, 416 F.3d at 1357 ("None of the cases to which the Board attributes the requirement of total DNA re-analysis, i.e., Regents v. Lilly, Fiers v. Revel, Amgen, or 12 Enzo Biochem, require a re-description of what was already known."). Thus, "[w]hen the prior art includes the nucleotide information, precedent does not set a per se rule that the information must be determined afresh."
>
> * * * *
>
> Indeed, a requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement.
>
> * * * *
>
> Indeed, the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification. Accordingly we hold that where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here "essential genes"), satisfaction of the written description requirement does not require either the recitation or incorporation by reference (where permitted) of such genes and sequences.

Applying the holding of Falkner to the present invention, it is clear that the application provides a clear written description of the claimed subject matter. In particular, Falkner holds that neither examples nor an actual reduction to practice of an invention are a prerequisite for fulfilling the written description requirement. Moreover, the present specification discloses more than one example of an embodiment of the invention, clearly demonstrating possession of an invention that works and is functional. Hence, applicant respectfully submits that this disclosure meets the requirements of § 112, first paragraph.

Furthermore, in accordance with "Falkner", a requirement to explicitly describe each and every embodiment possibly falling under the scope of the claims is an improper and impractical demand. The present specification discloses ample references (see pages 41 to 44), which represent only some of the literature examples that were known in the art at the time of filing the application. Based on the teaching of

the present invention in combination with the knowledge of a skilled artisan at the time of filing the application, it would have been possible without undue burden to arrive at the teaching of the present invention over the whole breadth claimed.

Thus, a skilled artisan, at the time of filing the application, could, for example, easily have determined which parts of a wild type coat protein are responsible for the incorporation of the wild type coat protein into the phage coat (See also in this respect page 6, last paragraph of the specification as filed which discloses corresponding assays). The same applies to the skilled artisan's ability to transfer the teaching as disclosed in the present specification for filamentous phages also to other non-filamentous phage systems, or, *mutatis mutandis*, to the ability to define fragments or functional fragments of a given (poly)peptide (See also in this respect page 10, first paragraph of the specification as filed, which further describes the functional fragments in connection with the present invention). Additionally, no further guidance is needed for a skilled artisan with respect to determining which peptide sequences might be used for purification and/or detection purposes. Although Falkner holds that working examples are not mandatory for complying with the written description requirement, the instant specification enumerates several alternatives for peptides that might be used in purification processes according to the present invention (See, for example, page 11 of the specification).

Finally, the Examiner asserts that the specification must disclose "common structural attributes that link together all of the claimed nucleic acid sequences" and "common attributes or characteristics that identify all of the members of the genus." See Office Action page 10, last sentence and page 11, second sentence, respectively. Applicant respectfully submit that phage coat proteins are well known in the art and that genes encoding modified coat proteins, and vectors containing those genes, also are well known in the art and that this commonality means that the claims fully comply with § 112, first paragraph.

Finally, it is not improper to utilize functional language in the claims in order to cover the breadth of the subject matter to which a is entitled:

> A functional limitation is an attempt to define something by what it does, rather than by what it is (e.g., as evidenced by its specific structure or specific ingredients). There is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper. *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971). (emphasis added)

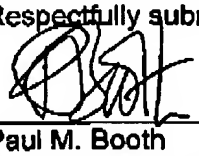
MPEP 2173.05. Accordingly, applicant respectfully requests withdrawal of the written description rejection.

CONCLUSION

In view of the foregoing amendments and remarks, applicant respectfully submit that the claims are in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-3840. **This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).**

Respectfully submitted,



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